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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/027,089	02/02/98	PRORTUGAL	F	CAB-001

HM12/1013

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EXAMINER	
SOUAYA, J	
ART UNIT	**PAPER NUMBER**
1655	12

DATE MAILED: 10/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/027,089	Dornburg
Examiner	**Group Art Unit**
Jehanne Souaya	1655

☒ Responsive to communication(s) filed on *Jul 25, 2000*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *9-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *9-18* is/are rejected.

☒ Claim(s) *9* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Currently, claims 9-18 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied (necessitated by amendment) or are reiterated. They constitute the complete set being presently applied to the instant Application. This rejection is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Objections

4. Claim 9 is objected to because of the following informalities: A claim number 9 appears two times in the amendment filed July 26, 2000. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. Claims 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Hammond et al (US Patent 5,374,718: Dec. 20, 1994) and Hogen (US Patent 5,714,321, 102(e) date: 2/22/94) and Anderson (Gene Probes 2: Hybridization Strategy, pp 1-29, Oxford University Press, New York, 1995) in view of Cilia et al (Mol. Biol. Evol., vol. 13, pp 451-461, 1996).

The claims are drawn to a method of determining the presence of an organism in a sample containing organisms of one or mor taxonomic groups by selecting a probe from an operon common to two or more organisms of the taxonomic groups, wherein the probe contains one or more base mismatches and wherein the probe is capable of discriminating between organisms by hybridization at two or more wash temperatures at or above the probes Tm, hybridizing the probe to the nucleic acid in the sample, and determining the presence or absence of hybridizing nucleic acid.

Methods of using probes to identify or differentiate closely related organisms was well known in the art at the time of the invention, as well as manipulations of reaction conditions to increase stringency, as can be exemplified by the teachings in the following three references. Hammond teaches hybridization assay probes specific for chlamydia pneumoniae which can distinguish c. pneumoniae form its most closely related taxonomic or phylogenetic neighbors (see col. 3, lines 35-40). Hammond teaches obtaining suitable probes for detection and discrimination.

Hammond generally teaches that all prokaryotic organisms (except for viruses) contain rRNA genes. Hammond teaches that variable regions of rRNA sequences from the 16S rRNA of chlamydia pneumoniae were identified by sequencing the rRNA of c. pneumoniae and its closely related phylogenetic neighbors and aligning the sequences to reveal areas of maximum homology and also alignment for regions of sequence variation (col. 3, lines 41-55). For construction of suitable probes, Hammond teaches that first, the stability of the probe:target nucleic acid should be chosen to be compatible with assay conditions, ie: hybridization involving complementary nucleic acids of higher G-C content will be stable at higher temperatures (col. 4, lines 51-65). Hammond teaches that ionic strength and incubation temperature under which a probe will be used, should be taken into account. Hammond teaches that incubation at temperatures below the optimum Tm may allow mismatched base sequences to hybridize and can therefore result in reduced specificity (col. 5, lines 8-15). Hammond further teaches that it is desirable to have probes which hybridize only under conditions of high stringency.

Hogan also teaches a method for preparing probes for use in qualitative and quantitative assays wherein the probes are capable of detecting and differentiating between eubacteria (see abstract). Hogan also teaches the hybridization of E. Coli probes to closely related organisms such as Shigella boydii, Sh. flexneri, Sh. dysenteriae, and Sh. sonnei (see col. 52, table 54). Hogan also generally teaches hybridization strategies, including variations in temperature, probe length, probe composition, and ionic strength in methods of identification of target nucleic acids (cols 7-11) and specifically points out that use of temperatures below the optimum (Tm) may

allow mismatched base sequences to hybridize and can therefore result in reduced specificity (col. 10, lines 21-24). Hogan also specifically teaches using filter hybridization methods, and the use of rRNA sequences in distinguishing between eubacteria (cols 1 and 2).

Anderson teaches hybridization strategies in constructing probes for methods of screening and identification. Anderson teaches factors affecting the rate of hybridization and the stability of hybrids, (p. 3-13) including probe length, composition, and temperature. Anderson specifically applies these manipulations to filter hybridization. Anderson also specifically teaches that to detect closely related family members, it is better to use stringent hybridization conditions followed by stringent washing conditions (for example, from the teaching of the previous three references, the ordinary artisan would be taught that such a condition could involve high temperature, etc) (p. 13, last sentence).

Although neither Hammond, Hogan, or Anderson teach using the probes of the instant invention, Cilia et al teaches sequence heterogeneities among 16S RNA sequences of E. Coli and Shigella (see abstract, and figure 3) and teaches nucleotide differences among Eubacteria by showing a line up of regions from 16S genes across species levels, showing the nucleotide sequence similarities and differences. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct the DNA sequences of the claimed invention for the use of probes and primers that could distinguish Shigella from E. Coli. Methods of distinguishing between different eubacteria using probes and primers that target regions of similarity and differences was readily known in the art at the time of the invention and

is exemplified by the Hogan patent. The ordinary artisan would have been motivated to construct probes and primers of the claimed invention to identify and differentiate E.coli from Shigella as Cilia teaches how closely related the two genus of bacteria are (see Fig 1). Cilia et al also teaches the variants of SEQ ID NOS 1, 2, and 4, (see FIG 3, and table 1), as well as most of the sequence of SEQ ID NO 4(see FIG 3, 1st row). [Applicant was faxed a copy of the results of a sequence search, which also discloses variants of SEQ ID NO 2, and the complete nucleotide sequence of SEQ ID NOS 1 and 4. This sequence search cites Cilia et al, identified above, as disclosing the accession numbers for these results (see table 1 of Cilia et al).] As the sequences of the 16S rRNA and rDNA sequences of the shigella species and E.coli sequences were known at the time of the invention, it would have been obvious for the ordinary artisan to construct probes and primers to regions of variability to be able to differentiate the closely related bacteria. Such methods were readily known in the art as is shown by the large amount of literature available in the art that identifies regions of variability among closely related bacteria for the purpose of constructing probes and primers useful in methods of differentiation.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. No claims as written are allowable over the prior art, although allowable subject matter does exist. As the examiner attempted to point out with the citation of a number of references that teach target nucleic acid (from closely related taxonomic groups using hybridization of probes to variable regions) identification and probe hybridization condition manipulations, the level of skill in the art at the time of the invention was extremely high, and routine manipulations of hybridization (and washing) conditions was well within the skill of the ordinary artisan. Furthermore, the art provides motivation for the artisan to manipulate conditions to achieve conditions of as high specificity and stringency as possible. Applicant's specification, however, teaches that some results are unexpected. Thus while applicant's general method is obvious (ie: claims 9-15), certain results are unexptected. The exact method steps outlined in the flow chart, including the specific sequences at each step of the method, are allowable, because such steps, in

the order used, gave unexptected results (sequences that were thought to hybridize with one organism, actually discriminated a different organism, which was unexptected). Applicant should note however, that an amendment sent in after final will not be entered if it raises new issues and requires further searching.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

Jehanne Souaya
Patent examiner
October 6, 2000